PRECIPITATION TEST : IT'S EVALUATION FOR EARLY DIAGNOSIS OF TUBERCULOUS MENINGITIS

THESIS

FOR

DOCTOR OF MEDICINE

(PEDIATRICS)

D548



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C E R T I F I C A T E

This is to certify that the work entitled "PRECIPITATION TEST : ITS EVALUATION FOR EARLY DIAGNOSIS OF TUBERCULOUS MENINGITIS", which is being submitted as thesis for M.D.(Paediatrics) examination of Bundelkhand University, 1993 by Pushpendra Kumar Bansal, has been carried out in the Department of Paediatrics.

He has put in the necessary stay in the Department, according to the University regulations.

Dated: 01 July, 1992

(RAMESH KUMAR) 1/7/92
M.D.,D.C.H.,
Professor and Head,
Department of Paediatrics,
M.L.B. Medical College,
JHANSI (U.P.).

C E R T I F I C A T E

This is to certify that the work entitled "PRECIPITATION TEST : ITS EVALUATION FOR EARLY DIAGNOSIS OF TUBERCULOUS MENINGITIS" has been carried out by Pushpendra Kumar Bansal, under my direct supervision and guidance in the Department of Paediatrics, M.L.B.Medical College, Jhansi.

The techniques and observations incorporated in this thesis have been undertaken by the candidate himself and checked by me from time to time.

Dated : 1st July 1992

(R.S. SETHI)
M.D.(Paed.),D.C.H.,
Assistant Professor,
Department of Paediatrics,
M.L.B. Medical College,
JHANSI (U.P.)

(SUPERVISOR)

ACKNOWLEDGEMENT

Today, at the culmination of the project, I look back into the past (the project has come a long way, in its history passing through difficult situations). It is the unflagging co-operation of a few that enabled it to see the light of the day. Without their whole-hearted support and never ending inspiration, the work could never have been successful. They provided helping hands in making the work run in the right track and when caught into trouble, to come out of it.

I wish to express my gratitude with obeisance to my respected Guide Dr. R.S. Sethi, M.D.,D.C.H., Assistant Professor, Department of Paediatrics, M.L.B. Medical College, Jhansi. His constructive criticism, worthy suggestions and valuable directions helped me to remain on the track to my goal.

I am highly indebted to my esteemed and learned teacher Prof. Ramesh Kumar, M.D.,D.C.H., Head of the Department of Paediatrics, M.L.B. Medical College, Jhansi, for his invaluable inspiration, definitive direction and keen interest in my work. His uncompromising commitment to medical ethics and untiring dedication to the patients have always been a tremendous source of inspiration to me.

I am grateful to Dr. (Mrs.) Sheela Longia, M.D., Associate Professor, Department of Paediatrics, M.L.B. Medical College, Jhansi, for her support and advice, which stood me in good stead. Her encouragement gave a new impetus to my work, whenever my enthusiasm slackened.

I am highly indebted to Dr. Anil Kaushik, M.D., Assistant Professor, Department of Paediatrics, M.L.B. Medical College, Jhansi, whose dynamic personality inspired me to work harder and his guidance always enlightened the path I had to cross in order to achieve the goal.

There are no words in the dictionary to express my gratitude to my venerate parents who provided me unending support and guidance in my upbringing. It is their inspiration and encouragement which has generated enthusiasm, confidence and spirit in me to achieve my goal and to survive through turbulent time.

The work couldn't have been completed without the painstaking efforts of my life companion, Poonam, who always helped me see the brighter side of things and boosted my morale even when the chips were down. From her I derived the emotional support, which helped me to tide over the crisis phases, that cropped up during the undertaking of the task.

It would be unfair to end the acknowledgement without expressing gratitude to all my friends and colleagues who even at odd hours extended their whole hearted support without any hesitation, taking the work as their own.

The role of the pretty, little innocent buds in making my work complete can hardly be exaggerated. It is to them that I owe my knowledge of Paediatrics.

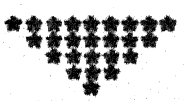
Last but not the least, I am also thankful to Mr. K.M. Thomas, for beautifully typing the manuscript and giving it the final shape.

P.K. Bansal

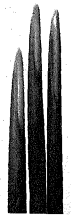
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INTRODUCTION



INTRODUCTION

Tuberculosis, from time immemorial, has remained a major public health problem, and is still rampant in the developing countries inspite of spectacular developments in the field of medical science. The annual rate of infection is about 3% and as stated by Ramra (1980), the prevalence of active disease is 15 to 25/1000 population. In India 40% of the children by the age of 16 are labelled as infected (Udani, 1983).

Tuberculosis is a disease of protean manifestations, almost involving each and every organ of the body and can be considered in the differential diagnosis of almost every disease.

It is well documented that children having primary infection are likely to go into progressive severe disease. Neurotuberculosis, especially TBM is considered to be the main cause of death amongst the various complication of primary infection. From the clinical/hospital practice, tuberculosis among children would continue to remain an important problem, because 50% of those admitted with tuberculosis in the hospital have TBM in the developing world. TBM is the most common type of meningitis in children between 9 months

to 5 years in the developing world. In TBM, despite the best available chemotherapy and supportive measures, prognosis for normality is poor if diagnosis is delayed. This can be gauged by the extensive study conducted by Udani (1983), who reported death due to CNS tuberculosis in 68.5% cases of total cases autopsied.

The diagnosis of TBM is based on certain essential as well as supportive criteria. The essential criteria are the typical physical, biochemical and cytological examination of CSF, while the supportive criteria are history of fever for 2 weeks or more, positive family history, mantoux positivity of 10 mm or more, radiologically positive and sputum positivity in older children. Although in majority of cases the essential and supportive criteria are sufficient to diagnose cases of tuberculous meningitis and to differentiate these cases from other meningitis, sometimes it becomes extremely difficult and challenging for the physician to diagnose cases of TBM from cases of partially treated pyogenic meningitis. In the last decade, certain immunological tests have been used to diagnose cases of meningitis, viz. NBT test, Bromide partition test and Elisa test, but all are non-specific and time consuming.

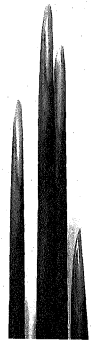
Levinson, emphasised the efficacy of a simple, easily performable, bed side test for the early diagnosis of cases of TBM, which could also help in differentiating

cases of tuberculous meningitis from that of partially treated pyogenic meningitis.

Upadhyaya et al (1984) was the first worker to perform this test for the early diagnosis of tuberculous meningitis, as well as to differentiate the cases of TBM from that of pyogenic meningitis. He, however, performed the precipitation test with slight modification of time temperature and concentration of the acid and the chloride used in the original method by Levinson. Later on Gupta et al (1990) also performed this test with similar modifications and confirmed its efficacy in the early diagnosis of TBM as well as in differentiating cases of TBM from that of pyogenic meningitis.

It is in the light of these observations, that the present venture has been undertaken to study in detail the incidence, modes of onset, various clinical presentation of cases of TBM and to perform the precipitation test for the early diagnosis of TBM, as well as to differentiate cases of partially treated pyogenic meningitis and other form of meningitis from that of tuberculous meningitis.

REVIEW OF LITERATURE



REVIEW OF LITERATURE

Tuberculosis is a major health problem in developing countries like India. It is one of the major killers in childhood. It involves different organs of the body. The most common form of tuberculosis is pulmonary tuberculosis, but the most dangerous one is that which affects the central nervous system. Tuberculous meningitis (TBM) is the commonest type of neuro-tuberculosis encountered in children in our country (Satya Gupta, 1981).

The frequency of tuberculous meningitis is closely related with the incidence of primary infection with tubercle bacilli. According to an ICMR survey the incidence of tuberculosis in India is about 1 in 50.

History of Tuberculosis :

Tuberculosis is a disease of antiquity. Well authenticated reports dating back to 5000 B.C. are available. Tuberculosis is described in Ayurveda and Rigveda as "Rajyakshma" and "Yakshma" respectively (Mittal, 1964). Yakshma means consumption, so for many years chronic form (consumption) was considered a degenerative or hereditory disease.

Tuberculosis was known in India even in pre-historic era. Hippocrates (470-377 B.C.) named it "Phthisis" which means wasting (consumption) or to dry up. Aristotle (500 - 400 B.C.) recognised the contagiousness of the disease.

In 18th century Richard Marton wrote the book "Phithisiologia" on tuberculosis. Laennec and his friend Gaspard Bayle (1810), in another study dissected dead bodies and found nodules in lungs, bones, intestine and even in the brain. Bayle (1810), declared that these nodules are the manifestation of disease and called these nodules tubercles and the disease, tuberculosis. Later Schollein (1839) also used the word tuberculosis for this disease.

Robert Koch in 1882 isolated Mycobacterium tuberculosis and established that this was the causative organism of the disease.

History of Tuberculous Meningitis :

Hippocrates (470-377 B.C.) described tuberculous meningitis (TBM) as "water on brain with headache". The first pathological description was given by Willis in 1682, when he noted tubercles on the swollen envelope of brain.

Robert Whytt (1768) published the first clinical description of tuberculous meningitis in his monogram

"Observations on the dropsy in the Brain". Charles Morehead (1849), described accurately the clinical picture and appearance at necropsy in cases of TBM, which incidentally is supposed to be the first well recorded description of TBM.

Mcgregor et al (1933 & 37) described the presence of tubercle bacilli in the CSF. The classic concept of pathogenesis of tuberculous meningitis was described by Rich and McCordock (1933).

Dastur & Udani (1965, 66, 70 & 71) published the pathology, pathogenesis and pathological and clinical correlation of tuberculous encephalopathy with or without meningitis. With the advent of CT scan various type of neurotuberculosis have been defined by Udani et al (1987).

Extent of the problem :

Tuberculosis continues to be a major health problem in developing countries. While its incidence has markedly diminished in developed countries of the world, there is no country which is free from this disease.

It has been estimated by sample survey conducted by I.C.M.R. (1955-58) that 40% of our population is infected with tuberculosis (they took the Mantoux positive cases as a criteria of infection). Later on this was

confirmed by another survey conducted by Raj Narain et al (1963). They also found that 1.8% are radiologically active and 0.4% are sputum positive. Prevalence of infection in children is 2% in 0 - 4 years and 16.5% in 10-14 years age group.

In India the annual rate of fresh infection in children is 4% (Raj Narain, 1980). Udani et al (1983) reported that 3.64 million children in age group of 0-4 years are infected annually. In another study Udani et al (1982) observed the prevalence of infection in children to be high viz., 40 percent children get infected by the age of 6 years and 80 percent get infected by the age of 15 years.

The problem of neurotuberculosis is much more severe. The incidence of TBM in a given community is directly proportional to the prevalence of tubercular infection in general.

Udani et al (1973) in his extensive work on CNS tuberculosis stated that the incidence of CNS tuberculosis was very high (42 - 46%) between 1950-60, while it came down to 28% during 1968-71. The fall in incidence as observed by him was not due to fall in cases of primary tuberculosis, but due to early diagnosis and better treatment of primary tuberculosis. Further, in a study of 3646 autopsies over a period of 10 years he

reported 9.8% cases of tuberculosis, out of these 65.5% had CNS tuberculosis and majority (81.5%) of these cases were suffering from meningitis.

Rao et al (1972) in another study, stated that the incidence of TBM varies from 1 - 4% among total inpatient admissions in different parts of India.

Benakappa et al (1975) in their study reported 47.4% cases of TBM, out of the total cases of tuberculosis seen by them. They also reported that the highest incidence of TBM was 34% in 3 - 5 years of age group.

Etiology :

Robert Koch (1882) isolated Mycobacterium tuberculosis as causative organism of tuberculosis. Acid fast nature was established by Ehrlich and acid fast staining was developed by Ziehl and Neelsen (1882). The human and bovine types of Myco-tuberculosis were distinguished in 1898 by T. Smith.

Mycobacterium tuberculosis is a slender rod, acid fast, non-motile, non sporing, aerobic bacteria. In majority of the cases the organism belongs to human type, atypical mycobacterium has also been reported to cause TBM (Joishy et al, 1969).

Pathogenesis :

TBM is never a primary manifestation but always occurs as a result of secondary hematogenous dissemination from the site of primary extra cranial tuberculous lesion which is frequently in the lungs. It usually occurs within first 6 - 12 months after the primary infection.

Till the study of Rich and Mc Cordock (1933) it was believed that tuberculous meningitis was a direct and immediate result of hematogenous infection of the meninges.

Rich and Mc Cordock (1933) postulated that tuberculous meningitis arises in two stages, first tuberculous lesions form in the brain or in the meninges from hematogenous dissemination of bacilli during the primary infection, then meningitis develops via discharge of bacilli and tuberculous antigens, from a caseous focus, directly into the subarachnoid space. Thus tuberculous meningitis is designated as meningoencephalitis.

Pathology :

The pathological picture of TBM depends upon the age of patient, virulence of organism and patient's state of immunity (Tandon et al, 1973). Besides the involvement of basal meninges, parenchymatous lesions of the brain are found due to direct extension of the inflammatory process or secondarily to vascular changes.

A thick exudate usually fills the interpeduncular and pontine cisterns (Dastur et al, 1973). The convexities of brain are relatively unaffected. The exudate surrounds the cranial nerves and the major blood vessels at the base of brain and often covers the choroid plexus. Vessels in the base of brain are involved and partial or complete occlusion may be seen. The histopathological changes in arteries reveals inflammatory, proliferative and degenerative changes (Winkelman & Moore, 1940). In meningeal veins, phlebitis may lead to thrombosis. The mechanism of vasculitis in TBM is not clear although the mononuclear cell infiltrates and fibrinoid changes of vessel wall suggest a delayed hypersensitivity reaction.

Dastur et al (1973), described six main gross parenchymal changes viz. ventriculitis, borderzone encephalitis, infarction, internal hydrocephalus, diffuse oedema and tuberculoma. It was observed by them that ventriculitis is less frequent than meningitis. Tubercles on the ependymal lining and choroid plexus are rare but are of diagnostic value. Borderzone encephalitis as reported by them is caused by impingement of exudate on the underlying brain parenchyma, it shows a variable degree of oedema, perivascular infiltration and microglial reaction. Infarction in their opinion, is caused by inflammation of vessels. It is due to arterial narrowing with or without total occlusion causing infarction of the

zone supplied by artery, mostly the middle cerebral artery. The vascular lesions cause various types of hemiplegia, seizures and mental retardation.

They further opined that internal hydrocephalus is a frequent feature of TBM which most of the time is of the communicating variety, resulting from blockage of the basal cisterns by inflammatory exudate or by arachnoid adhesions. Less common type is obstructive caused by narrowing or occlusion of the aqueduct or by blockage of outlet foramina of the fourth ventricle. The narrowing of aqueduct is due to oedema of mid-brain or compression of the brain stem by surrounding meningeal exudate.

Diffuse oedema is important cause of diffuse brain damage and is seen in the absence of cerebral infarction.

Diagnosis of Tuberculous Meningitis :

Early diagnosis is important because prompt and adequate treatment reduces mortality and morbidity. The diagnosis is established with the help of clinical picture, history of contact, examination and certain supportive investigations viz. routine blood examination, tuberculin test and radiography and confirmed by CSF examination both cytological, biochemical and culture of Myco-tuberculosis.

Clinical Manifestation :

The onset of TBM is usually insidious with vague symptomatology, but it may also be acute occurring within a span of just six days. The classical course and clinical picture of the disease seen these days is quite variable as the patient usually presents to us quite late and the symptomatology has been altered by antimicrobial therapy.

British Medical Council (1948) delineated three stages of the disease, as the classical presentation.

Stage I - Prodromal phase. It consists of vague ill health, mild fever, irritability, loss of weight, loss of appetite and headache. There are no definite neurologic signs and symptoms. This stage lasts for 1 - 2 weeks.

Stage II - It is characterised by appearance of definite neurological signs, signs of meningeal irritation with slight or no clouding of consciousness with or without cranial nerve palsies.

Stage III - Severe clouding of consciousness, stupor or coma, repeated convulsions, tremors with variable pareses. Decerebrate rigidity, optic atrophy, bruxism (teeth grinding), nystagmus may be present.

Symptomatology :

Fever : Fever is one of the most common manifestation in cases of TBM. While Illingworth (1956) reported its incidence to be 38%, Ramchandran et al (1970), Udani et al (1974), Benakappa et al (1975) reported a much higher incidence of fever in their study, viz. 68.4%, 74.2% and 98% respectively.

Headache : Headache is another important manifestation reported by various workers in cases of TBM especially in children above the age of 3 to 4 years. Illingworth (1956) & Lincoln (1960) reported a much higher incidence of headache (73% and 70% respectively), than most of the Indian authors (Bharucha et al, 1969; Benakappa et al 1975) who reported the incidence of headache to be markedly less than the incidence observed by foreign authors viz. 16.6% and 10% respectively.

Vomiting : It is another common manifestation of TBM specially in children below 3 years of age. Udani et al (1974) reported vomiting as presenting manifestation in 42% of cases, while Illingworth (1956) & Benakappa et al (1975) reported a higher incidence in their cases viz. 80% and 46% respectively.

Convulsions : Convulsions are one of the most important features usually observed in later stages of disease but may also be presenting manifestation in atypical cases

of TBM (Udani et al, 1974). The author opined that convulsions may be due to cerebral oedema or due to occlusion of large arteries and further said that the prognosis of cases of TBM is dependent on the nature and duration of convulsions, cases of intractable convulsions having the most poor prognosis.

Udani et al in 1974 reported convulsions as presenting manifestation in 47.4%, Benakappa et al (1975) reported convulsions in 46% of cases. Illingworth (1956) however reported its incidence to be much higher viz. in 80% of cases.

Altered Sensorium : It is a frequent finding in cases of TBM. Ramchandran et al (1970) noted its incidence in 41.9% cases at the onset of disease, while Udani et al (1974) and Benakappa et al (1975) reported altered sensorium as presenting symptom in 22% and 44% cases respectively.

History of contact : It is very important to elicit the history of contact with a tuberculous patient. Manchanda et al (1966), Ramchandran et al (1968), Bhakoo (1969), Udani et al (1971) and Magotra et al in 1974 reported positive contact history in 30%, 10%, 15%, 25.3% and 19.5% of cases respectively.

Examination :

Specific emphasis was given by nearly all the workers on certain important findings on general examination besides conducting a detailed neurological examination. Anaemia, lymphadenopathy, hepatomegaly were some of the important features observed by many of the workers in the field (Ramchandran, 1968; Inderjeet Singh, 1974; Benakappa et al, 1975).

Ramchandran (1968) in his detailed analysis of 1284 cases reported anaemia in 23%, lymphadenopathy in 24% and hepatomegaly in 7.3% of cases.

Signs of meningeal irritation viz. nuchal rigidity and Kernig's sign were one of the constant features noticed by various workers. While Bharucha et al (1969) recorded the incidence of signs of meningeal irritation only in 45%, Udani et al (1974) & Benakappa (1975) observed a more or less similar incidence of signs of meningeal irritation viz. 82% and 84.8% respectively, which was seen to be much higher than that observed by Bharucha et al.

Minor and major neurological deficits have been reported differently by the various workers. Bharucha et al (1969) reported cranial nerve palsies in 24% and hemiplegia in 16.6% cases.

Udani et al (1974) has however given a detailed description of various minor and major neurological deficit. They observed optic atrophy in 14.2%, ophthalmoplegia in 5.4%, VIth nerve palsy in 10.8% and VIIth nerve palsy in 29% cases. Among the major neurological deficits hemiplegia and quadriplegia were observed in 19.6% and 19.2% cases respectively, while monoplegia and paraplegia had a very low incidence of 2.6% and 0.6% respectively. Hydrocephalus was reported clinically in 30.14% of their cases which was confirmed radiologically in their study.

Benakappa et al (1975) observed VIIth nerve palsy in 14%, hemiplegia in about 22% and hydrocephalus in 12%, which is more or less equal to the incidence of these deficits given by Udani et al (1974).

Fundus Examination :

Fundus examination has been reviewed in detail by nearly all the workers who have done clinical study of cases of TBM. Mishra in the year 1962 reported changes in the fundus in 50% of study group cases, while Verma (1966) reported these changes only in 30.6% cases. In a later study Thapar et al (1968) also reported more or less similar involvement as reported by Mishra (1962).

Three important changes have been reported by all these workers, viz. papillitis, optic atrophy and

papilloedema. It was observed that papillitis was the commonest manifestation reported by all these workers (23.3%, 12.3% and 25% respectively) followed by optic atrophy (21.66%, 9.2% and 11%). Papilloedema was however reported in lesser number of cases, viz. 5%, 7.6% and 13% respectively. Choroid tubercle was not a very common finding and was reported only in 1.5% cases by Verma (1966).

Udani et al in the year 1974 reported changes in the fundus in only 14% of cases, while Benakappa et al in the year 1975 reported changes in fundus in 24% cases. However, both these workers have not specified the exact changes of fundus examination.

Investigations :

Haematological : Nearly all the workers who have done detailed clinical and pathological examination in cases of TBM have reported anaemia and increased ESR as a significant concomitant finding. Kimsey (1948) reported that acute cases of TBM, as in any other infection have a predominance of polymorphonuclear leucocytosis which is gradually replaced by lymphocytes as the disease progresses. Similar findings have also been reported by many other workers in the field.

Tuberculin Test : Robert Koch in 1890 demonstrated for the first time that the extract of tubercle bacilli can evoke a skin reaction in sensative individual which may be characteristic for the disease.

In 1907 Von Pirquet described a skin test which could be used in clinical work for the detection of those sensitised to tuberculin. He was the first worker who introduced the term allergy to explain the altered reaction in form of cutaneous reaction.

Mantoux introduced a classical intradermal test in 1910 by using 0.5 ml of 1 : 5000 of old tuberculin with trichloracetic acid.

In 1934 Florence Seibert coined the term purified protein derivative for the product obtained by protein precipitation with trichloracetic acid from Koch's tuberculin.

There are several methods of tuberculin testing like Mantoux test, Von Pirquet test, Vollmer Patch test, Heaf Multiple puncture method, Moro's percutaneous test, but among all of these Mantoux test is most popular and is in common practice.

Mantoux Test :

It is an intradermal test introduced by Mantoux in 1908. This test is performed by injecting 0.1 ml of

standard solution of tuberculin by tuberculin syringe with 26 or 27 gauge needle into the clean skin of the flexor aspect of left forearm.

Induration is read after 48 - 72 hours. The correct time to read Mantoux reaction is on 3rd day (Mande, 1954).

American lung association, New York (1969) recommended the following interpretations to diagnose a case of tuberculosis.

An induration of 10 mm or more is to be taken as positive reaction without any doubt, while induration of 5 - 9 mm is to be considered as doubtful reaction, in such cases other evidences of tuberculosis should be searched to make a final diagnosis of tuberculosis. An induration of 4 mm and below shows a negative reaction.

A positive Mantoux test is an evidence that the person has been infected with tubercle bacillus and is allergic or hypersensitive to its proteins. A false negative reaction may also occur in several conditions like faulty technique, advanced stage of the disease, malnutrition or due to administration of corticosteroid or immunosuppressive agents.

Miller et al (1963) noted that tuberculin reaction was positive in almost all cases (93.6%) unless

the child was moribund. While Udani et al in the year 1962 reported Mantoux negativity in 20% cases.

In a later study Bhakoo and Gupta (1969) observed Mantoux negativity in 16.6%. On the other hand Ramchandran et al (1970) reported a very high percentage of Mantoux negative cases i.e. 64%, the explanation of high incidence of Mantoux negativity given by Ramchandran was, that cases brought to their hospital were in advanced stage of disease with malnutrition and also because the test dose was only 1 T.U. Similar results were observed by Benakappa et al in the year 1975. Kandari & Udani (1977) observed Mantoux positive cases in 45.4% of cases.

C.S.F. :

Since the CSF examination is key to the diagnosis of TBM, much emphasis has been given by nearly all the workers on this aspect. A greater percentage of cases of TBM manifest with typical CSF finding, i.e. rise in protein 50 - 200 mg%, a rise in cellular element (20 - 500 cells) which principally are lymphocytes (though in acute stages polymorphonuclear leucocytes may predominant), and a decrease of both sugar and chloride to a varying degree depending on the stage of the disease. However, few cases do occur which reveal no significant abnormality.

Nearly all the workers have reported normal or atypical changes in the CSF in some of the cases of TBM.

While Bharucha et al (1969), Ramchandran et al (1970) and Udani et al (1974) have reported normal CSF findings in more or less equal number of their study group cases viz. 16.4%, 16.5% and 16% respectively. Mehta et al (1975) and Benakappa et al (1975) reported normal CSF in 6% and 8% of cases respectively.

Bacteriological diagnosis :

Demonstration of Mycobacterium Tuberculosis in CSF :

Microscopic examination of CSF for acid fast bacilli is the most important procedure for a definite diagnosis. The frequency with which organism are seen varies widely depending on both the time devoted to searching and the number of specimens examined. Since in practice this is not possible, tubercle bacilli are hardly found in 3% of cases (Udani, 1974).

The low incidence of AFB demonstration is due to antituberculous treatment which cases of TBM have often received before coming to the hospital and also due to different pathogenesis of the disease in children, where allergy plays a much more important role (Dingley et al, 1937).

Inspite of difficulties encountered in demonstration of tubercle bacilli in CSF, surprisingly, Stewart (1953) and Illingworth (1956), recorded a very

high percentage of detection of tubercle bacilli in cases of TBM viz. 91% and 85% respectively. This was possible in their study by making a thick smear from centrifuged specimen of CSF. Demonstration of AFB in CSF varies from 2.2 to 79% of cases by various workers in their series. Udani et al (1946) reported 30% AFB positive cases on smear examination made from cobweb, while Thapar (1969) reported only 10% incidence.

Isolation of tubercle bacilli from the CSF varies with different techniques, 3% by ordinary centrifuge method, 38.8% by precipitation of the deposit from CSF by alcohol, 57.4 - 79% by floatation hydrocarbon technique (Mukherjee and Udani, 1964; Thapar, 1967).

Culture of C.S.F. for Myco-tuberculosis :

The CSF is collected in a sterilized vial after lumbar puncture and is cultured on Lowenstein Jensen medium. The growth of Myco. tuberculosis is observed at the end of the third week. If no growth occurs it is further incubated upto 8 weeks. Failure to grow the organism indicates very low content or absence of Myco. tuberculosis in CSF or faulty technique.

Dingley (1974) reported culture positive cases in 5.1% of cases, while Benakappa et al (1975) reported a very high percentage of culture positive cases i.e. 54%.

Radiography :

The demonstration of primary foci in the lung is an important supportive investigation in cases of TBM. Hence most of the workers have evaluated the radiological findings. The lesions which have been demonstrated vary from active to dormant primary focus, to progressive primary complex and to diffuse infiltration in the lungs.

Lincoln (1960) and Lee & Brown (1968) have reported a definite primary foci in the lung in 80% and 90% of cases respectively. Ramchandran et al (1970), Udani et al (1974) and Benakappa et al (1975) reported a definite tubercular lesion in lung viz. 52.2%, 28.8% and 46% cases respectivaly. Ramchandran, further specified the lesion in the lung and reported diffuse infiltration in 28.8% and milliary tuberculosis in 7.7% of cases.

Levinson Test for TBM :

TBM presents as protean manifestation and the early diagnosis depends on history, clinical features and examination of CSF. The diagnosis of tuberculous meningitis can be made with certainty by demonstration of causative agent in smear prepared from deposits, culture on LJ media and animal inoculation of CSF. These are not only time consuming but are also difficult to demonstrate in majority of cases.

Although in most of the cases the diagnosis of TBM can be easily confirmed by clinical and pathological investigations, some of the cases of PTPM (partially treated pyogenic meningitis) pose a great problem in diagnosis. A simple and rapid precipitation test (modification of Levinson's method), however comes to our aid and rescue in differentiating such cases.

Principle : Levinson test is based upon the principle that a characteristic ratio may be obtained between the alkaloidal precipitate formed by sulfosalicylic acid and the metallic precipitate formed by mercuric chloride in tuberculous meningitis. Positive reactions are indicative of tuberculous meningitis.

Procedure :

1. Into each of two small test tubes of uniform length and width place 1 ml CSF.

2. To one add 1 ml of 3% sulfosalicylic acid in water and to the second 1 ml of 1% mercuric chloride in water.

3. Shake the tubes and allow to stand at room temperature for 24 hours. The height of the sediments is then measured in millimeters.

4. Under normal conditions the sediment in both tubes is very slight. In all suppurative meningitis, the amount of sediment in the sulfosalicylic acid tube is very

large often being three times the size of sediment occurring with mercuric chloride. In TBM the opposite occurs, the precipitate with mercuric chloride being usually three times larger than that obtained with sulfosalicylic acid.

5. The two precipitate are of different character, that of the acid is heavy and compact and starts to form immediately, while that of the chloride is light, feathery and forms slowly. Sometimes the precipitate does not settle down so the tubes are shaken well 2-3 hr before making a final reading. For diagnostic purposes it is not the amount of protein which settles down in the two precipitates but the relative height of the sediments in millimeters in the two tubes.

6. If no precipitate forms, use a 2 percent mercuric chloride solution and a 6 percent sulfosalicylic acid solution.

The protein in normal CSF is composed of 80% albumin. In pathologic state with an increase in protein the high normal albumin globulin ratio is reduced. Changes in the albumin globulin ratio influence the total protein when sulfosalicylic acid is employed.

Precipitation test :

This test was performed with slight modification of temperature and time in Levison's method in order to

have an early diagnosis. This modified technique was first innovated by Upadhyaya et al (1984).

The CSF samples were taken in duplicate tubes and mixed with equal volume of 3 percent sulfosalicylic acid (SSA) and 6 percent solution of mercuric chloride (Hg cl2) respectively. The samples were kept at 37°C for ½ hr, then at 4°C for 2 hrs and height of precipitation column was noted. The test was interpreted as positive for the diagnosis of TBM when the height of precipitate column was three times more in mercuric chloride than that of sulfosalicylic acid. It is a qualitative test of proteins as the qualitative differences in the alubmin and globulins of the CSF may be of value in differentiating between TBM and other forms of meningitis.

Upadhyaya (1984), was the first worker in recent times to have conducted a study to differentiate cases of TBM where the clinical and investigative findings have no correlation with each other. He selected 120 cases of meningitis for the study. He divided all cases into three groups.

Group A - where the cytological and biochemical findings were not correlating with the clinical diagnosis of TBM.

Group B - where CSF findings were in correlation with clinical diagnosis of TBM, which served as positive control.

Group C - cases of pyogenic meningitis which acted as negative control.

Age group of the patients for the study ranged from 3 months to 12 yrs of age. It was seen that maximum number of cases were in the age group of 0 - 4 yrs (38%) followed by 5 - 9 yrs (33%) and 9 - 12 yrs (29%). The workers also observed that there was male preponderance in their study (53.3%). The main presenting features observed by them were high fever with or without convulsions in majority of cases. Other features were headache, vomiting and altered sensorium.

CSF was examined in detail for cytobiochemical examination in all cases. It was observed that the CSF was clear in 35% of cases, turbid in 50% of cases and a cob-web formation was found in only 15% of cases. Further, it was seen that nearly 53% of cases had cellular content of more than 100 cells/cmm, 35% had a cellular content ranging from 51-100 cells/c.mm, whereas 12% had cellular content ranging from 4 - 50 cells/c.mm. On further analysis it was seen that 54% of cases had predominence of lymphocytes only, 14.5% had predominence of only polymorphs, while a mixed cellular picture was seen in 31.5% of cases.

CSF sugar which has great prognostic value was found to be normal in 31.6% of cases, decreased

below 45 mg% in 55%, while 13.3% cases had sugar content below 20 mg%.

Similarly, it was seen that 23.4% of cases had normal value of Protein; 43.3% had values more than 45 mg%, and 33.3% had protein values more than 100 mg%.

The precipitation test was performed in 75 cases. CSF samples were taken in duplicate tubes and mixed with equal volume of 3% sulfosalicylic acid and 6% solution of mercuric chloride respectively. The samples were then kept at 37°C for ½ hr. at 4°C for 2 hrs and height of precipitation column were noted. The test was interpreted as positive for the diagnosis of TBM when the height of precipitation column was three times more in mercuric chlorine test tube than that observed in sulfosalicylic acid test tube. He observed that in Group A where the CSF findings were not in correlation to the clinical diagnosis of TBM, this test was positive in 86.5%, whereas in group B where CSF findings were in favour of the clinical diagnosis of TBM (which served as positive control group) it was positive in 93.5% of cases, while in group C (cases of pyogenic meningitis) the test was negative in 86.5% of cases. He therefore opined that the test is an affective, sensitive and specific and can be performed even at the peripheral centers.

Recently Gupta et al (1990) conducted an extensive study on this subject after many years to evaluate the significance of precipitation test for early diagnosis of TBM. Their case material consisted of 125 children between the age group of 3 months to 12 yrs, which were divided into three groups. Group A consisted of 50 cases where CSF findings were not in correlation to the clinical diagnosis of TBM. Group B consisted of 50 cases where CSF findings were consonent with the clinical diagnosis of TBM (positive control) and group C consisted of 25 cases of pyogenic and other meningitis except TBM. This group acted as negative control for the study. In addition to the detailed history, clinical examination, laboratory investigation and detailed CSF examination (cytobiochemical and bacteriological) a modified Levinson's precipitation test was performed in all the cases.

They observed that maximum number of their patients were in the age group of 5 - 9 years with a higher percentage of disease in males (54%) than females (46%). The main presenting features noted by them were high fever, convulsions, altered sensorium, vomiting, headache, apathy and irritability.

On a detailed examination of CSF the workers noted that in group A the CSF was turbid in 56% of cases, while in 24% of cases the CSF was clear. Cob-web formation

was noticed in 64% of cases. 24% of cases in group A showed normal protein contents while maximum number of cases (52%) showed a protein content between 45 - 100 mg% and in rest of the cases (24%) it was more than 100 mg%. Sugar content was found to be normal in 20% cases, while mild decrease (20 - 45 mg%) was noticed in 64% cases and rest 16% cases showed a marked decrease (less than 20 mg%). Chloride content was decreased only in 36% cases.

All the cases in group A showed an increased cell count in CSF. Maximum number of cases (44%) showed a cell count between 5 - 50, followed by 36%, where it was more than 100 and in 20% cases the count was between 50 - 100/c.m. On differential analysis of cells in the same group, maximum number of cases (56%) showed a mixed type of picture i.e. lymphocytes and polymorphs both, while in 36% there were lymphocytes only and only polymorphs were reported in 8% of cases. Workers did not find any AFB positive case in group A.

In group B maximum CSF samples (88%) were found turbid on naked eye examination. Cob-web formation was noticed in 96% of cases. On biochemical study all the cases were having increased protein, out of which 96% were having protein content more than 100 mg%. Sugar content was normal in 4%, mild decrease was seen in 62% and marked decrease was observed in 34%. Chloride content was normal in 60% cases. On cytological study, cell count

was increased in all the cases, in 16% it was in the range of 5 - 50, 44% cases were having cell count between 50 - 100 cells/c.m. and rest (40%) were having cell count of more than 100 cell/c.m. On differential study of cells, maximum number (60%) were having only lymphocytes, 36% cases showing mixed picture, while only 4% were having only polymorphs.

In group C (cases of pyogenic meningitis) 68% of cases exhibited turbid CSF and cob-web was present only in 4% cases. On biochemical study protein content was normal in 8%, while it was increased mildly in rest (92%) of cases. Sugar content was normal in 12% of cases while it was mildly decreased in rest of the cases (88%). Chloride content was normal in 92% of the cases. On cytological examination, all the cases were having increased cell count. In 40% cases the cell count was between 5 - 50, in 44% between 50 - 100 and in 16% cases were having more than 100 cells/c.m. On differential study of the cells majority of the cases (72%) showed polymorphs only, while in rest of the cases mixed cellularity was found.

After doing a detailed cytobiochemical examination all the CSF samples were subjected to precipitation test (modified Levinson's method). Workers found that in group A (where CSF finding were not in favour of clinical

diagnosis of TBM) 92% cases had positive precipitation test, in group B, proven cases of TBM (positive control) test was positive in 96% cases while in group C (cases of pyogenic meningitis) it was negative in 96% of cases.

On the basis of their extensive study, the workers concluded that the precipitation test for early diagnosis of TBM is easy to conduct, less time consuming and specific.

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MATERIAL AND METHODS

MATERIAL AND METHODS

The present study was conducted in the Department of Paediatrics, M.L.B. Medical College, Jhansi, over a period of 1 year from March 1991 to February 1992. The study was primarily aimed to evaluate the role of precipitation test in the early diagnosis of tuberculous meningitis, its significance in diagnosis of those cases where the CSF findings were not in favour of the clinical diagnosis of TBM and its value in differentiating cases of pyogenic meningitis and other types of meningitis from cases of tuberculous meningitis.

Accordingly on the basis of history, general and systemic clinical examination, investigations, all suspected cases of meningitis of varying etiology, severity and duration admitted in the Paediatrics ward formed the basis of our study.

Our case material was broadly divided into three sub-groups.

Group A : CSF findings not in correlation with clinical diagnosis of TBM.

Group B : CSF findings consistent to the clinical diagnosis of TBM (taken as positive control).

Group C : CSF findings and clinical diagnosis in favour of pyogenic meningitis and other type of meningitis except TBM (taken as negative control).

Selection of cases :

Group A :

This group comprised of 25 cases, where on the basis of mode of onset, prolonged history, evidence of signs of meningeal irritation and other neurological deficit, there was a strong suspician of TBM, but the CSF findings were not in favour of the typical findings found in cases of TBM, viz., rise of protein (100 to 500 mg), sugar (less than 50 mg%) and cells (predominently lymphocytes).

Group B :

This group consisted of 50 cases of TBM. Here the clinical diagnosis and suspician of TBM was substantiated by typical CSF findings observed in cases of TBM. This group, therefore acted as positive control in the evaluation of the precipitation test.

Group C :

This group comprised of 25 cases of pyogenic meningitis. This group served as negative control to evaluate the false positive reaction of the precipitation test.

Diagnosis :

The diagnosis of all the cases of meningitis was based on a detailed history, examination, supportive investigations and confirmed by biochemical and cytological picture of CSF.

History :

A detailed present, past and family history was recorded in each and every case.

In most of the cases, history given by the parents was of few days, but further interrogation revealed that the onset was insidious, and the child was unwell for the last 1 to 2 months.

The typical history in a classical case of TBM was that the child had become irritable, cranky, had a marked decrease in appetite, had low grade fever for the past couple of weeks unresponsive to medications prescribed by the local practitioners. There was also history of vomiting and headache (7 3 yrs.) in most of the cases. Convulsions, deterioration in consciousness and neurological deficits were recorded in majority of the cases and were the reason for hospitalisation.

Due emphasis was given to elicit the history of exanthematous fever, pertussis and head injury in the past. History of contact was also obtained in each and every case.

BCG status of the child was inquired from mother and confirmed by looking for BCG scar on left deltoid region.

Due consideration was given to observe the socio-economic status, as assessed by the per capita income of the parents.

Physical examination :

A thorough general and systemic examination was conducted in each and every case and the findings were recorded on the pre-designed proforma.

Due emphasis was given to record the anthropometric measurements in each case and the cases were then divided, as those having normal weight for age and those having Protein energy malnutrition, according to the classification of Nutritional Sub-committee of Indian Academy of Paediatrics (1972).

Head circumference was measured with the help of a measuring steel tape, to find the norms and to exclude any evidence of hydrocephalus.

During general examination, due emphasis was given to look for lymphadenopathy, anaemia, subcutaneous fat and any evidence of muscle wasting to delineate cases of PEM.

A detailed neurological examination was done in each and every case. Due emphasis was given to categorise cases according to the degree of unconsciousness into grade I, II, III and IV. Besides conducting a thorough cranial nerve examination, a detailed motor and sensory examination was done to find out various neurological deficits. In all the children signs of meningeal irritation were noted, while in children below 1 year bulging anterior fontanelle was taken as an evidence of raised intra-cranial tension. Crack pot sign was also elicited to denote evidence of increased intra-cranial tension.

Superficial and deep reflexes were recorded in each case. Cerebellar and extra pyramidal involvement in the form of abnormal movements were also seen wherever necessary.

Examination of the respiratory system and GIT system was done in detail in each and every case. Due emphasis was given to assess the presence or absence of hepatosplenomegaly.

Fundus examination was carried out in detail in all the cases after dilating the pupils with 10% Drosyn eye drops.

Investigation :

After taking a detailed history and doing a thorough examination, following investigations were performed :

1. Routine Blood Examination : Total leucocyte count (TLC), Differential leucocyte count (DLC), Haemoglobin estimation, and Erythrocyte sedimentation rate (by Wintrobe's method) were done in each and every case.

2. Mantoux test : Mantoux test was done in group A & B. In the mantoux test 0.1 ml of 5 T.U. of PPD was injected intradermally on the volar surface of cleansed left forearm with the help of tuberculin syringe fitted with 26 gauge short needle. Successful intradermal injection was considered by raising up of small pale wheel like elevations of the skin about 6-10 mm in diameter.

The reaction was recorded after 72 hrs of injection in good light. The indurated skin was palpated and the largest transverse diameter of induration was recorded in millimeters.

Interpretation :

Cases with induration of 10 mm or more were regarded as positive, 5 - 9 mm was taken as doubtful and 0 - 4 mm was taken as negative reaction.

3. Radiography : Skiagram chest (P.A. view) - It was done in all the cases to look for evidence of primary complex and progressive primary tuberculosis as well as to see caseous bronchopneumonia and milliary involvement.

Skiagram skull : It was done in cases where there was clinical evidence of hydrocephalus or there was a suspicion of intra-cranial tuberculoma.

C.S.F. :

After doing lumbar puncture in every case of meningitis CSF was collected. The colour, turbidity and tension of CSF was noted and then cytobiochemical examination was performed. Sugar was estimated by the method of Asatoor and King (1954), protein estimation was done by Turbidimetric method and chloride content was also measured by titration method. Cell count was done in Neubauer's chamber and expressed per cubic millimeter.

To differentiate the cells CSF smear was prepared and stained by Leishman stain.

Demonstration of Mycobacterium tuberculosis by Ziehl-Neelsen Staining :

CSF was allowed to stand at room temperature for one hour. In some cases where Cob-web coagulum was formed a smear was prepared from it otherwise the specimen

was centrifuged. Supernatant was discarded and the smear was made from the deposits. After fixation the smear was stained by Ziehl-Neelsen method.

The whole slide was flooded with carbol fuschsin and the slide was heated from below till the steam started coming out. The slide was then kept for 5 - 10 minutes, so that proper staining could be achieved. Stain was thrown and the slide was rinsed in water. Decolourisation was done with 20% sulphuric acid till on washing with water the smear retained a faint pink colour. Then counter-staining was done with methylene blue for 1 minute. Slide was rinsed in water, allowed to dry in air and was examined under oil immersion. Mycobacteria when present, appeared as bright red rods against a blue background.

Culture on Lowenstein Jensen Media :

The CSF was transferred to a sterile centrifuge tube and was then centrifuged. The supernatant was discarded, a loopful of the deposits was innoculated on a slope of Lowenstein Jensen medium. The slopes were incubated in an upright position at 37°C. They were examined at weekly intervals for maximum period of 8 weeks. Any growth that took place was confirmed by staining with Ziehl-Neelsen method.

Precipitation Test :

All CSF samples in our study were subjected to precipitation test by the modified Levinson test (Kolmar, 1969).

Equal amount of CSF (i.e. 1 ml) was taken in two small test tubes of uniform length & width. Thereafter, in one test tube, 1 ml of 3% sulfosalicylic acid and in other test tube 1 ml of 6% mercuric chloride was mixed with CSF. Both the test tubes were incubated for ½ an hour at 37°C, followed by incubation at 4°C for 2 hours. The height of precipitated column was then measured in mm in both test tubes. Positive results were indicated by three times more height of precipitated column in test tube having CSF with 6% mercuric chloride than the test tube having CSF with 3% sulfosalicylic acid, while negative results were interpreted when the height of precipitated column was three times in sulfosalicylic acid tubes than the test tube containing CSF mixed with mercuric chloride.

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OBSERVATIONS

OBSERVATIONS

The present study was conducted in the Department of Paediatrics, M.L.B. Medical College, Jhansi, over a period of one year from March 1991 to February 1992.

The main aim of our study was to evaluate the role of precipitation test in the early diagnosis of TBM. Further, an attempt was made to assess its significance in the diagnosis of those cases of TBM where the CSF findings were not consonant to the clinical diagnosis of TBM, as well as to ascertain its value in differentiating cases of pyogenic meningitis and other forms of meningitis, from tuberculous meningitis.

It was also our endeavour to study the incidence, the mode of onset, various clinical features, a detailed neurological examination, to elicit the pattern of various major and minor neurological deficits and to assess the nutritional status in our group of children which primarily belonged to low socio-economic group of Bundelkhand region.

The incidence of tuberculous meningitis of the total paediatric admissions in our study was observed to be 1.7%.

Table I depicts the various study groups. A total of 100 cases were examined in the present study.

25 cases belonged to group A (CSF findings not correlated to clinical diagnosis of TBM), 50 cases belonged to group B (CSF findings and clinical diagnosis in favour of TBM), which served as positive control and 25 cases were of group C (CSF findings and clinical diagnosis in favour of pyogenic meningitis) which served as negative control in our study.

Table I

Showing various study groups.

Sl. No.	Study group	No. of cases
1.	A : CSF findings not correlated to clinical diagnosis of TBM	25
2.	B : CSF findings and clinical diagnosis in favour of TBM (Positive control)	50
3.	C : CSF findings and clinical diagnosis in favour of pyogenic meningitis (Negative control)	25

Table II shows age distribution of the cases in various study groups.

An attempt was made to divide our case material into various age groups in order to observe the age incidence of cases of TBM and to compare it with that of pyogenic meningitis (which served as negative control).

It is evident from Table II, that out of 25 cases in group A, the highest incidence was found in 1-3 yrs age group (52%), followed by 24% below 1 yr and 12% each in the age group 4-6 yrs and 7-12 yrs respectively. Similarly, in group B which comprised of 50 cases of TBM the highest incidence was again observed in 1-3 yrs (38%), followed by 24% in age groups below 1 yr, and 4-6 yrs respectively and the incidence was much less (14%) in 7-12 yrs age group. In pyogenic meningitis (group C) the highest incidence in our study was however observed in 7-12 yrs age group (44%) followed by 28%, 20% and 8% in the age group below 1 yr, 1-3 yrs and 4-6 yrs respectively.

Table II

Showing age incidence.

Age in yrs	Group A (25 cases)		Group B (50 cases)		Group C (25 cases)	
	No.of cases	%	No.of cases	%	No.of cases	%
Below 1 yr.	6	24%	12	24%	7	28%
1 - 3 yrs.	13	52%	19	38%	5	20%
4 - 6 yrs.	3	12%	12	24%	2	8%
7 - 12 yrs.	3	12%	7	14%	11	44%

Table III depicts the sex of our various study groups. It is clearly evident from the table, that in all the groups, males predominated and the incidence was found to be much higher than females.

Table III

Showing sex of various study groups.

Sex	Group A (25 cases)		Group B (50 cases)		Group C (25 cases)	
	No.of cases	%	No.of cases	%	No.of cases	%
Males	17	68%	29	58%	19	76%
Females	8	32%	21	42%	6	24%

Table IV depicts mode of onset of disease in various study groups.

TBM is a disease which has a variable mode of onset. In view of this we categorised our case material according to mode of onset as, acute, subacute and chronic cases. The acute cases were taken as those which presented to us within 6 days, subacute were categorised as those having onset from 7 days onwards to 3 weeks and chronic cases were those who presented after more than three weeks duration.

It was observed in our study that in group A, 52% cases had a chronic mode of onset, 44% had subacute onset, whereas only 4% cases presented atypically where the mode of onset was acute. Similarly in group B, it was observed that the mode of onset was mainly subacute and chronic in 54% and 40% cases respectively, whereas 3 cases (6%) presented atypically as acute cases. On the contrary

in cases of pyogenic meningitis (group C) maximum number of cases (64%) had an acute onset and 36% had subacute onset of disease. None of the cases of group C in our study had a chronic mode of onset.

Table IV

Showing onset of disease in various study groups.

Study groups	Acute (1-6 days)		Sub-acute (7 days - 3 weeks)		Chronic (more than 3 weeks	
	No.of cases	%	No.of cases	%	No.of cases	%
Group A : CSF findings not correlated to clinical diagnosis of TBM	1	4%	11	44%	13	52%
Group B : CSF findings and clinical diagnosis in favour of TBM	3	6%	27	54%	20	40%
Group C : CSF findings and clinical diagnosis in favour of pyogenic meningitis	16	64%	9	36%	-	-

The clinical features of various study group cases have been shown in Table V. A striking observation of our study was that 100% cases in all the three groups had fever which was naturally the most common presenting symptom. Convulsions and unconsciousness were the other

two important common features in all the three groups of cases as is evident in Table V. Vomiting was another common presentation in 64% of cases in group A and B, whereas it was present in 80% cases of pyogenic meningitis (group C). Headache was present only in 30% of cases in TBM group above 3 yrs of age, whereas it was present in 36% cases belonging to group C.

Table V

Showing presenting symptoms at the onset.

Symptoms	Group A: CSF findings not correlated to clinical diagnosis of TBM		Group B: CSF findings in favour of clinical diagnosis of TBM		Group C: CSF findings and clinical diagnosis in favour of Pyogenic meningitis	
	No.of cases	%	No.of cases	%	No.of cases	%
Fever	25	100%	50	100%	25	100%
Headache (above 3 yrs.)	7	28%	15	30%	9	36%
Vomiting	16	64%	32	64%	20	80%
Convulsions	22	88%	47	94%	22	88%
Unconsciousness	20	80%	40	80%	19	76%

Relevant past history was recorded in all the cases with special emphasis to elicit the history of contact, history of measles and history of whooping cough.

It was seen (Table VI) that 52% of cases of TBM in group A had a positive history of contact with tuberculosis, 28% had past history of measles, however none of the cases gave history of whooping cough in this group. In group B, 30% cases had a positive history of contact, 14% cases had a prior history of measles and 2% gave history of whooping cough. In cases of Pyogenic meningitis (Group C) there was no past history of measles and whooping cough.

Table VI

Relevant past history.

	Group A: CSF findings not in favour of clinical diagnosis of TBM		Group B: CSF findings in favour of clinical diagnosis of TBM		Group C: CSF findings and clinical diagnosis in favour of pyogenic meningitis	
	No.of cases	%	No.of cases	%	No.of cases	%
History of contact with tuberculosis	13	52%	15	30%	-	-
Measles	7	28%	7	14%	-	-
Whooping cough	-	-	1	2%	-	-

It is evident from table VII that all the cases of TBM in both groups A and B had varying degrees of malnutrition according to the classification of Indian

Academy of Paediatrics (1972). Accordingly it was seen (Table VII) that maximum number of cases in group A (52%) had grade II malnutrition followed by 24% and 16% and 8% in grade III, I and grade IV malnutrition. Similarly, in group B, grades of malnutrition had an almost similar pattern as in group A as depicted in the table. However in group C, 5 cases (20%) had normal nutrition, whereas 44% belonged to grade II and 24% and 12% belonged to grade I and grade III malnutrition respectively.

Table VII

Showing grades of malnutrition in various groups.

Study groups	Grades of Malnutrition							
	Grade I		Grade II		Grade III		Grade IV	
	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
Group A: CSF findings not correlated to clinical diagnosis of TBM	4	16%	13	52%	6	24%	2	8%
Group B: CSF findings in favour of clinical diagnosis of TBM	5	10%	27	54%	12	24%	6	12%
Group C: CSF findings and clinical diagnosis in favour of pyogenic meningitis	6	24%	11	44%	3	12%	-	-

It was our endeavour to specially observe certain important clinical features in each group of our cases as has been depicted in Table VIII.

Anaemia was found to be a very common clinical manifestation in cases of tuberculous meningitis (group A and B). It was observed in 88% cases of group A and 78% cases in group B. However, group C (cases of pyogenic meningitis) had nearly half the incidence of anaemia (40%) as compared to the cases of TBM.

Lymphadenopathy was another common feature seen more in cases of TBM than in pyogenic meningitis. It was seen (Table VIII) that though lymphadenopathy was observed in 40% and 36% cases of group A and group B respectively, it was present only in 16% cases of pyogenic meningitis.

Special emphasis was also given to assess enlargement of liver in each and every case. It was seen that the incidence of hepatomegaly was 38.6% in cases of TBM, as compared to 32% in cases of pyogenic meningitis. Mostly the enlargement was of mild to moderate degree ranging from 2 to 4 cm. Consistency of liver was found to be firm in all the cases, however, there was no evidence of Jaundice in any of these cases.

Mild splenomegaly was observed in 13% and 8% cases of TBM and pyogenic meningitis respectively.

Table VIII

Showing some important clinical findings in various study groups.

Findings	Group A		Group B		Total cases of TBM in Gp.A& B		Group C	
	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
Anaemia	22	88%	39	78%	61	81%	10	40%
Lympha-denopathy	10	40%	18	36%	28	37%	4	16%
Hepato-megaly	12	48%	17	34%	29	38.6%	8	32%
Spleno-megaly	4	16%	6	12%	10	13%	2	8%

Neurological examination has been depicted in Table IX.

Signs of meningeal irritation were found to be present in higher percentage of cases (96%) in pyogenic meningitis as compared to that observed in the TBM group (74%). On the contrary, cranial nerve palsies were present in 24% of cases in TBM group, as compared to only 8% observed in pyogenic group. The commonest cranial nerve involved was VIIth nerve followed by VI & III in both group A and B. However, only VIIth nerve was affected in pyogenic group manifesting cranial nerve palsy. Motor deficit too, had a much higher incidence in cases of TBM, both in group A and B, than that observed in pyogenic group as depicted in Table IX.

An attempt was also made to evaluate the different grades of coma. It is evident from table IX that most of the cases in both group A and B had grade III coma (40% and 38% respectively), followed by grade II coma in 32% and 28% cases and grade I coma only in 4% and 10% cases of group A and B respectively. In pyogenic meningitis however, most of the cases (48%) were admitted in grade II coma, followed by 16% and 12% in grade I and III respectively.

Table IX

Showing various neurological signs.

Signs	Group A		Group B		Total TBM cases in group A & B		Group C	
	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
Signs of meningeal irritation	19	76%	37	74%	56	74%	24	96%
Cranial Nerve Palsy	5	20%	13	26%	18	24%	2	8%
VIIth N.	4	16%	11	22%	15	20%	2	8%
VIth N.	2	8%	3	6%	5	6.6%	-	-
IIIrd N.	-	-	2	4%	2	2.6%	-	-
Motor deficit	5	20%	13	26%	18	24%	1	4%
Grades of Coma								
I	2	4%	5	10%	7	9.3%	4	16%
II	8	32%	14	28%	22	29.3%	12	48%
III	10	40%	19	38%	29	38.6%	3	12%
IV	-	-	2	4%	2	2.6%	-	-

Table X depicts various hematological findings in our study groups. It is evident from table, that though the mean total leucocyte count in group B was found to be higher than group A, no statistical significant difference was seen in both these groups (p value $\nearrow 0.05$). In group C the total leucocyte count was much higher than in group A and B (TBM group) and these values were found to be statistically significant (p value AC $\swarrow 0.05$, p value BC $\swarrow 0.05$) from that observed in both groups A and B.

A significant finding of our study, as evident from the table, is that as expected, there was polymorphonuclear leucocytosis in group C (pyogenic group) while there was lymphocytosis in both groups A and B, viz., TBM groups. On statistical analysis of the differential count it was seen that the polymorphonuclear count in the pyogenic group was statistically higher and significant ($p_{AC} \swarrow 0.001$, $p_{BC} \swarrow 0.001$) from both groups A and B and vice-versa, the lymphocyte count in both groups A and B was higher and statistically significant from group C ($p_{AC} \swarrow 0.001$, $p_{BC} \swarrow 0.001$).

Regarding the mean hemoglobin values it was observed, that cases of pyogenic meningitis (group C) had higher mean values than both groups A and B and the values were found to be significant (p value AC $\swarrow 0.001$, $p_{BC} \swarrow 0.001$). However, no statistical significant difference was seen in mean Hb values between group A and B ($p_{AB} \nearrow 0.05$).

The mean ESR on the other hand was highest in group B and no statistical difference was seen in mean ESR values between group A and B ($p_{AB} > 0.05$). However, in group C the ESR was found to be much lower than TBM groups, values being statistically significant ($p_{AC} < 0.05$, $p_{BC} < 0.01$).

Table X

Showing various important haematological values.

Investigation	Group A (n = 25) Mean ± S.D.	Group B (n = 50) Mean ± S.D.	Group C (n = 25) Mean ± S.D.
Leucocyte count	10210 ±1648.37	10454 ±2037.0	11696 ±2360.8
Haemoglobin	8.8 ± 1.73	9.3 ± 0.87	10.5 ± 1.33
Erythrocyte Sedimentation rate	39.3 ±11.64	41.2 ±13.84	28.1 ±20.60
Polymorphonuclear leucocyte count	36.8 ± 3.84	36.7 ± 4.05	64.4 ± 6.49
Lymphocyte count	62.3 ± 3.83	61.5 ± 4.29	33.0 ± 8.79

Table X(A)

Showing results of statistical significance of various Haematological values.

Comparison between groups	Total Leucocyte count		Hemoglobin		E.S.R.		Polymorphs		Lymphocytes	
	t-value	p value	t value	p value	t value	p value	t value	p value	t value	p value
A vs B (df=73)	0.46	>.05	1.64	>.05	0.581	>.05	0.101	>.05	0.784	>.05
A vs C (df=48)	2.53	<.05	3.82	<.001	2.317	<.05	13.596	<.001	14.964	<.001
B vs C (df=73)	2.14	<.05	4.61	<.001	3.213	<.01	17.87	<.001	18.627	<.001

The findings of tuberculin test and X-Ray chest have been depicted in table XI.

The overall Mantoux positivity in cases of TBM (both groups A & B) was 34%, though it was slightly higher in group A (40%) than in group B (32%).

X-Ray findings consistent to the diagnosis of primary tuberculosis was observed in 60% cases in TBM group, of which 76% cases were positive in group A and 52% cases were positive in group B.

X-Ray chest was done only in 15 out of the 25 cases of pyogenic meningitis and all were found to be normal.

Table XI

Showing some important supportive investigation findings.

Investigation	Group A		Group B		Total TBM cases		Group C	
	No.of cases	%	No.of cases	%	No.of cases	%	No.of cases	%
Mantoux test positive	10	40%	16	32%	26	34%	-	-
X-Ray findings consistent with the diagnosis of tuberculosis	19	76%	26	52%	45	60%	-	-

Ophthalmological examination was done in each and every case to observe the findings of papillitis, papilloedema and primary optic atrophy. It is seen from table XII, that papilloedema was observed in 16% cases of group A, while primary optic atrophy was seen in 8% in this group. None of the cases had evidence of papillitis. Similarly, papilloedema and primary optic atrophy were observed in 6% and 8% cases in group B respectively and here again none of the cases had papillitis. Cases of pyogenic meningitis in contrast revealed no abnormality.

Table XII

Showing findings of ophthalmological examination.

Groups	Fundus Changes					
	Papillitis		Papilloedema		Primary optic atrophy	
	No.of cases	%	No.of cases	%	No.of cases	%
A	-	-	4	16%	2	8%
B	-	-	3	6%	4	8%
C	-	-	-	-	-	-

A detailed physical, biochemical and cytological examination of CSF was conducted in each and every group of cases. As expected in tuberculous meningitis, on naked eye examination CSF was found to be clear in 96% and 100% cases of group A & B respectively. However in group C, 44% of cases showed turbidity on naked eye examination, as against only 4% observed in group A in the TBM group. Coagulum formation was only seen in group C in 8% cases.

As already stated, group A consisted of 25 cases in which the CSF findings were not consistent with the clinical diagnosis of TBM. Accordingly in this group with regard to the CSF finding, it was observed that many of these cases had normal protein or a very high protein content and the sugar was either normal or very much

decreased. Another significant criteria of delineating these cases in group A, was that most of these cases had a mixed cellular content (lymphocytes + Polymorphs) and some even had only polymorphonuclear leucocytosis in CSF, as against the typical findings of predominance of lymphocytes in the CSF which is the usual picture in CSF in cases of TBM.

It is evident from table XIII that in group A 24% cases had normal protein values (15 - 45 mg%), 16% had protein content more than 45 mg%, 40% had protein content between 100-500 mg%, while 20% cases had protein content of more than 500 mg%.

A significant finding in sugar content in group A was that 40% of clinically diagnosed cases of TBM had normal sugar values (45-90 mg%) while another 32% had extremely low values (below 20 mg%). Similarly, it was seen, that as against the decreased values of CSF chloride usually seen in CSF in typical case of TBM, 80% of group A cases showed normal chloride level in CSF.

Another important observation in this group was that nearly 64% of cases had a mixed cellular content (lymphocytes and polymorphs). 16% had polymorphonuclear leucocytosis and only 20% of these cases had a usual picture of lymphocytes.

The CSF findings in group B (positive control cases where CSF findings were consistent to the clinical diagnosis of TBM) are clearly seen in table XIII. It is evident from table, that 64% of these cases had protein content of 100-500 mg%, 34% of cases had levels ranging between 45-100, whereas in this group we had only 1 case (2%) which showed normal protein content (15-45 mg%).

As expected 36 out of the 50 cases in this group (72%) had decreased sugar level ranging from 20-45 mg% while 12% of cases had extremely low levels viz. $\angle$ 20 mg%. However, 16% of cases had normal CSF sugar levels.

54% of group B cases had decreased chloride content, whereas 46% had normal chloride values more than 750 mg%.

The clinching CSF finding that categorised the cases into group B was, that all the cases in this group (100%) had only lymphocytes in the CSF.

The CSF finding in group C (Pyogenic group) revealed predominence of polymorphs in 92% of cases, a decreased sugar level below 20 mg% in 72% of cases, and protein content varying from 100-500 mg% and more than 500 mg%, in 72% and 24% of cases respectively. As expected because of acute nature of this group 80% had normal chloride values.

Table XIII

Showing CSF findings in various study group cases.

Findings	Group A No.of cases	%	Group B No.of cases	%	Group C No.of cases	%
Physical :						
Clear	24	96%	50	100%	14	56%
Turbid	1	4%	-	-	11	44%
Coagulum	-	-	-	-	2	8%
Biochemical :						
Protein						
15- 45 mg% (Normal)	6	24%	1	2%	-	-
45-100 mg%	4	16%	17	34%	1	4%
100-500 mg%	10	40%	32	64%	18	72%
7 500 mg%	5	20%	-	-	6	24%
Sugar :						
Normal 45-90 mg%	10	40%	8	16%	4	16%
20-45 mg%	7	28%	36	72%	3	12%
∠ 20 mg%	8	32%	6	12%	18	72%
Chloride :						
Normal 7750 mg%	20	80%	23	46%	20	80%
Decreased ∠ 700 mg%	5	20%	27	54%	5	20%
Total cell count :						
5 - 50 cells/ C.mm.	12	48%	10	20%	1	4%
50 - 100 "	8	32%	22	44%	3	12%
7 100 "	5	20%	18	36%	21	84%
Lymphocytes only	5	20%	50	100%	-	-
Lympho + Polys	16	64%	-	-	2	8%
Polys only	4	16%	-	-	23	92%

The primary aim of our study was to do the precipitation test in cases of tuberculous meningitis and to arrive at an early diagnosis in those cases of TBM where the CSF findings were not in favour of clinical diagnosis of TBM. The results of precipitation test done in all the three groups of cases are depicted in Table XIV. A very significant finding of our study was that in group A, 96% of cases showed a positive precipitation test as measured by three time increase in the column of mercuric chloride, as against that observed in the sulfosalicylic tube. Only 1 case (4%) in group A had a negative reaction to the precipitation test. Our positive control, viz., group B, which were easily diagnosed by the CSF picture, had a 98% positivity in precipitation test. In all the 25 cases of group C in which precipitation test was done, the precipitation test was negative in all the cases (100%). Here the sediment in sulfosalicylic acid tube was three times the size of sediment, observed in the tube containing mercuric chloride.

Table XIV

Showing results of precipitation test.

Groups	Precipitation test			
	Positive		Negative	
	No.of cases	%	No.of cases	%
Group A : CSF findings not correlated to clinical diagnosis of TBM	24	96%	1	4%
Group B : CSF findings consistent with clinical diagnosis of TBM (Positive control)	49	98%	1	2%
Group C : CSF findings and clinical diagnosis in favour of pyogenic meningitis (Negative control)	0	0	25	100%

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DISCUSSION

DISCUSSION

The present study was carried out in the Department of Paediatrics, M.L.B. Medical College, Jhansi, over a period of one year from March 1991 to February 1992.

The study was aimed to evaluate the role of precipitation test in the early diagnosis of TBM, in differentiating cases of pyogenic meningitis and other forms of meningitis from the TBM group and more importantly to assess the significance of precipitation test in the diagnosis of those cases of TBM where the CSF findings were not consonant to the clinical diagnosis of TBM. Study was also aimed to assess in detail the mode of onset, various clinical features and to carry a detailed neurological examination in each and every case. Accordingly with these objectives in view our case material was selected and broadly divided into three groups to assess the specificity and significance of the precipitation test in TBM group and the group comprising of cases of pyogenic meningitis.

In the light of observation depicted in Tables I - XIV, following inferences have been drawn and discussed in detail.

A total of 100 cases of meningitis were examined in the present study (Table I). As already detailed in the observations, 25 cases (group A) were cases of TBM, where the CSF findings were not correlating to the clinical diagnosis of TBM, and 50 cases (group B) were also cases of TBM in which CSF as well as the clinical findings were in favour of diagnosis of TBM, and acted as positive control. The remaining 25 cases (group C) were cases of pyogenic meningitis, which served as negative control in our study.

For the past two decades umpteen workers have delved to study in detail the various clinical presentation of neurotuberculosis. Bharucha et al (1969) were one of the earlier workers in recent times to have conducted a study to elucidate the various clinical features of TBM in 24 cases. However, later workers like Ramchandran et al (1970) and Udani et al (1974) reviewed cases of TBM and their clinical features very extensively in 288 and 500 cases respectively. Benakappa et al (1975) in a later study took up 50 cases for discussion of cases of TBM.

All these above mentioned workers took up the conventional tools for diagnosis of TBM in their study but none of these workers attempted to arrive at an early diagnosis of TBM by the precipitation test.

Upadhyaya et al (1984) were the first Indian workers to have attempted to arrive at an early diagnosis of TBM by way of the modified version of precipitation test as given by Levinson. He conducted this test in 75 cases of meningitis.

Gupta et al (1990) were the last workers who used this simple test in the early diagnosis of TBM in 125 cases.

Both the above workers divided their case material in three groups comprising of 30, 30 and 15 cases in group A, B and C by Upadhyaya et al (1984) and 50, 50 and 25 cases in group A, B and C respectively by Gupta et al (1990).

Further an attempt was made to categorise the various cases of TBM in different age groups. It is evident from Table II, that maximum incidence of TBM was observed between 1-3 yrs of age, while the maximum incidence of pyogenic meningitis was observed in 7-12 years age group. Of the total 75 cases of TBM, a significant finding observed by us was, that 24% of cases of TBM presented below 1 year of age, while 28% of cases presented below 1 year of age in the pyogenic group. Our findings of increased incidence of TBM between 1-3 years of age and decrease in incidence as age advances has also been reported by many other workers in the field.

Ramchandran et al (1970) in his study reported 65% of cases between 1-4 yrs age group and only 10% cases below 1 year. Udani et al (1974) and Benakappa et al (1975) like us, have also reported nearly similar incidence of TBM (60%) in 1-5 yrs of age group. Our incidence of 24% in TBM cases presenting below 1 year, is more or less similar to that reported by Udani et al (1974) and Benakappa et al (1975) viz. 18.6% and 26% cases respectively.

We observed a higher incidence (44%) between 7-12 years age group in pyogenic meningitis as most of the cases admitted in our ward were cases of meningococcal meningitis.

In our study we observed a preponderance of male children in all the study group cases than females as is depicted in Table III. A similar higher incidence of male children in TBM has been reported by Bharucha (1969), Ramchandran (1970), Udani (1974) and Benakappa (1975), viz. 70.8%, 63%, 56% and 60% respectively.

Upadhyaya et al (1984) and Gupta et al (1990) in their study had also a similar male preponderance of 53.3% and 54% respectively.

TBM as already mentioned has got a variable mode of onset and presentation. In view of this, an attempt was made to categorise our cases according to the

mode of onset in three groups viz., acute (presenting to us within 6 days), subacute (onset between 7 days to 3 weeks), and chronic (onset of more than 3 weeks duration). It is evident from table IV, that in group A (where CSF findings were not correlating with the clinical diagnosis of TBM) 52% cases had a chronic mode of onset, whereas 44% and 4% had subacute and acute course respectively. Group B (cases of TBM where CSF findings and clinical diagnosis were in favour of TBM) also showed a more or less similar mode of onset viz. 40% and 54% as chronic and subacute variety, whereas only 6% cases in this group presented atypically as acute cases. As usual, most of the cases (64%) in the pyogenic group had an acute mode of onset, while 36% cases in this group presented to us as subacute cases.

Only Udani et al (1974) and Benakappa et al (1975) have in recent times commented on the mode of presentation in cases of TBM. Both these workers, unlike us, have reported a much higher incidence of acute presentation viz. 41.8% and 28% respectively in their study.

On the contrary, though we observed a higher incidence of cases with chronic mode of presentation, Udani et al (1974) and Benakappa et al (1975) reported chronic onset in 35.6% and 34% cases respectively.

Clinical features were studied in detail in all the cases as depicted in Table V. It is evident from table V, that fever, convulsion, unconsciousness and vomiting were the commonest clinical features in decreasing incidence in our cases. Fever was found to be present in all the cases (100%). Convulsions were present in 88% and 94% cases in group A and B and 88% in group C, whereas unconsciousness was seen in 80% cases in both group A and B and 76% cases in group C. Vomiting was found to be a more common feature in cases of pyogenic meningitis (80%), as against 64% cases in TBM group. Headache was noted in 30% cases in TBM group above 3 years of age, whereas it was present in slightly higher percentage (36%) in pyogenic group.

Bharucha (1969) and Benakappa (1975) reported fever in 91.6% and 98% cases respectively, these percentages are more or less similar to that reported by us. Ramchandran (1970) and Udani (1974) however reported fever as presenting symptom in 68.4% and 74% cases respectively. Similarly, convulsions and vomiting were the presenting symptoms in more or less equal percentage of cases in our study as well as in the studies conducted by Bharucha and Benakappa. However, Ramchandran et al (1970) and Udani (1974) reported convulsions as a presenting symptom in a fewer percentage of cases viz. 54.8%, 47.4% and vomiting in 36.9% and 42% cases respectively, than that observed in our study.

Table VI depicts the relevant past history in all three groups of cases. Special emphasis was given to elicit the history of contact, history of measles and history of whooping cough. It was seen, that in group A positive history of contact was elicited in 52% of cases and measles in 28%. However, none of the cases had history of whooping cough. In group B however history of contact was positive in 30% of cases, 14% cases had history of measles and 2% had history of whooping cough.

Bhakoo et al (1969), Ramchandran et al (1970), Magotra et al (1974) and Benakappa et al (1975) elicited the history of contact in 15%, 10%, 19.5% and 16% which is much less than that reported by us.

A high incidence of contact, observed by us, as against incidence of Bhakoo et al (1969), Ramchandran et al (1970), Magotra et al (1974) and Benakappa et al (1975) is easily explainable since tuberculosis has attained enormous proportions and is rampant in Bundelkhand region of Uttar Pradesh.

Bhakoo et al (1969) recorded history of measles and pertussis in 22% and 18% of cases respectively, whereas Magotra et al (1974) and Benakappa et al (1975) observed history of measles in 3% and 16% cases respectively and history of pertussis in 13% and 2% cases respectively.

An attempt was made in our study, to classify the cases into different groups of malnutrition according to the classification of Indian Academy of Paediatrics (1972). A significant finding was, that all the 75 cases of tuberculous meningitis were malnourished. In the pyogenic group however, 20% had normal nutrition whereas 80% were malnourished. Since most of the cases in group A and B viz. TBM group had subacute and chronic mode of onset and had been ill for many weeks, it was seen that 54% cases belonged to grade II and 24% belonged to grade III in both group A and B respectively. A striking feature as expected was, that none of the cases in pyogenic group had grade IV malnutrition which was however present in 8% and 12% of cases in group A and B. We however could not arrive at any direct correlation between the severity and the chronicity of the cases of TBM to that of the different grades of malnutrition.

Since none of the workers have classified their data into different grades of malnutrition according to Indian Academy of Paediatrics, we have not been able to compare our results with those of other workers. Ramchandran et al (1968) however were the only workers who classified their case material into marasmus and kwashiorkor. Out of 1284 cases in their study, 31 cases were of kwashiorkor and 23 cases were of marasmus.

It was our endeavour to observe certain common and important clinical features in each group which have been depicted in table VIII. Majority of the cases in group A and B had mild degree of anaemia, though anaemia was not a very significant finding in most of the cases of pyogenic meningitis.

Ramchandran (1968) however reported anaemia in only 23% cases of TBM, as against our observations of 81% in TBM. High incidence of anaemia in our study is easily explainable since majority of our cases had grade II and III degree malnutrition (54% and 24%) in TBM group.

Another common clinical finding in the TBM group was significant lymphadenopathy in 40% and 36% cases of group A and B, while lymphadenopathy was noted only in 16% of cases in the pyogenic group. Ramchandran et al (1968) however, reported lymphadenopathy in 24% of cases.

Due emphasis was given to note the enlargement of liver and spleen in each and every case. In our study we observed hepatomegaly in 38.6% cases of TBM and only 32% cases of pyogenic meningitis. The enlargement of liver ranged from 2 to 4 cm, it was firm in consistency and there was no evidence of clinical jaundice. Splenomegaly on the other hand was seen in 13% in TBM group and 8% in pyogenic group.

The enlargement of liver in tuberculosis has been reported by various other workers in the field. Ramchandran (1968) unlike us, has observed hepatomegaly in only 7.3% of cases.

The high incidence of hepatomegaly as observed by us may be due to the accompanying grade II and grade III malnutrition in nearly 54% and 24% of cases respectively, as well as due to direct involvement of liver by tuberculous process.

The important findings of neurological examination which was done in detail in each case has been depicted in table IX. As expected, signs of meningeal irritation were present in greater number of cases of pyogenic meningitis (96%), as against 74% seen in the TBM group.

Udani et al (1974) and Benakappa et al (1975) have reported more or less similar incidence of signs of meningeal irritation (84.8% and 82% respectively) in their study. However, Bharucha et al (1969) reported these signs only in 45% of their cases.

A striking feature of our study was a greater incidence of cranial nerve palsies and motor deficits in the TBM group vis-a-vis that of the pyogenic group. While cranial nerve involvement was observed in 24% of cases (18 cases) in TBM group, it was present only in 8% cases in pyogenic group.

It is evident from the table, that the common cranial nerve involvement were VIIth nerve, followed by VIth nerve and IIIrd nerve in our study. 15 cases (20%) had VIIth nerve involvement, 5 cases (6.6%) had VIth nerve palsy, whereas only 2 cases (2.6%) had IIIrd nerve palsy. Another finding worth mentioning here is that, 4 cases of TBM had multiple cranial nerve involvement. Of these 4 cases, 3 cases had involvement of both VIIth and VIth nerve, whereas one case had three cranial nerve involvement viz. IIIrd, VIth and VIIth nerve.

Various workers in the past have reported different cranial nerve palsies in their study group. Agarwal and Kumar (1969) reported IInd nerve involvement in 44% and VIIth nerve involvement in 28% cases, their percentage being slightly higher than that observed by us. Bharucha et al (1969) gave a total incidence of cranial nerve palsies in 25%, without making any reference to the differential involvement of the cranial nerves. This incidence is more or less equal to that reported in our study.

Udani et al (1974) gave a detailed analysis of cranial nerve palsies. He reported highest incidence of VIIth nerve palsy in 24%, followed by IInd nerve in 14.2%, VIth nerve involvement in 10.8% and IIIrd nerve involvement in 5.4% of cases. Our findings of different cranial nerve palsies are more or less similar as observed by Udani et al (1974).

Benakappa et al (1975) have reported the involvement of VIIth nerve in 24% of cases, IInd nerve in 24% of cases and VIth nerve only in 2% of cases. Thus it is evident from all the above studies including us, that VIIth cranial nerve is maximally involved in cases of TBM, followed by IInd nerve, VIth nerve and last of all IIIrd nerve.

Motor deficits (predominantly hemiplegia) were found in 24% of cases in TBM group, as against 4% cases in pyogenic meningitis. Our findings of hemiplegia in 24% of cases are more or less similar to that reported by Udani et al (1974) and Benakappa et al (1975) of 19.6% and 22% respectively. Bharucha (1969) however reported hemiplegia in 12.5% of cases. Few other workers, viz. Miller (1963), Manchanda (1966) and Agarwal & Kumar (1969) have reported a much higher incidence of hemiplegia in their study 35%, 38% and 36.5% respectively.

It is evident from Table IX that 38.6% of cases in TBM group had grade III coma, followed by grade II coma in 29.3% of cases, grade I in 9.3% of cases and grade IV coma in only 2.6% of cases. 15 cases in TBM group were found to have normal level of consciousness. In pyogenic meningitis most of the cases (48%)were admitted in grade II coma, 6 cases in this group were also found to have normal consciousness.

None of the workers in the past have graded coma and hence it is not possible for us to compare the grades of coma to that observed by other workers.

Bharucha et al (1969) recorded that only 50% of cases in their study were unconscious. Udani et al (1974) on the other hand reported a high incidence of semi/unconsciousness in 81% of cases and drowsy in 17.4% of cases. One percent of cases in their study were conscious on admission. Benakappa et al (1975) found that most of their cases were semi-conscious or unconscious (60%) on admission and 36% were found to be drowsy. Our findings of unconsciousness of different grades, in 80% of cases in TBM, is more or less similar to that reported by Udani et al (1974). The different incidence of unconsciousness as reported by various workers may be due to different stages of the disease on admission in different series.

The hematological values in different study groups (Table X) revealed, that the mean total leucocyte count in the pyogenic group was statistically higher than the values observed in both groups of TBM. As expected in our study too, there was lymphocytosis in TBM group and polymorphonuclear leucocytosis in the pyogenic group.

The mean haemoglobin concentration in the pyogenic group was higher and statistically significant ($P_{AC} < 0.001$, $P_{BC} < 0.001$) than observed in both TBM groups.

However, no statistical significant difference was seen in the mean haemoglobin value in both group A and B ($p_{AB} > 0.05$).

On the other hand the mean ESR values were much higher and statistically significant in both group A and B than that observed in pyogenic group ($p_{AC} < 0.05$, $p_{BC} < 0.01$).

The details of hematological values have not been given by any of the other in past and hence an exact comparison could not be done. The presence of lymphocytosis, increased erythrocyte sedimentation rate (ESR) and decreased haemoglobin in cases of TBM is well explained by the subacute and chronic nature of the cases selected for our study.

Diagnosis of tuberculosis in our study was corroborated by doing the tuberculin test and X-Ray chest in all the cases of TBM. It was seen that the overall Mantoux positivity in the cases of TBM in our study was to the extent of 34%, which was found to be slightly higher in group A (40%) than in group B (32%).

Many workers in the past have substantiated the diagnosis of tuberculosis by doing the tuberculin test. Benakappa et al (1975) and Kandari & Udani (1977) have, like us, reported nearly similar Mantoux positivity in cases of TBM viz. 36% & 45.4% respectively.

Lothe et al (1973), Jaiswal & Bhandari (1976) and Chandra & Chaudhary (1977) have reported a slightly higher incidence of Mantoux positivity than that reported by us viz. 53.2%, 57%, 50% respectively.

The high rate of Mantoux negativity seen in our study is easily explainable, as nearly 75% cases of TBM group were having grade II and grade III malnutrition and most of our cases were in advanced stage of disease. Since many of the cases were perhaps also on steroids prior to admission, it was also one of the factor of negative Mantoux response. X-Ray chest which was done practically in all the cases revealed primary tuberculosis in 60% of the total group of TBM cases.

Many of the workers have also extensively studied extra-cranial involvement of tuberculosis in children with TBM. Udani et al (1974) reported primary tuberculosis and hilar adenitis in 46% cases, miliary shadows in 17.6%, abdominal tuberculosis in 3.2% and spinal tuberculosis in 0.6% of cases. Benakappa (1975) had reported more or less similar incidence as reported by Udani (1974).

Lincoln (1960) and Ramchandran et al (1970) in their work however observed a very high incidence of intra-thoracic tuberculosis viz. 80%, 75% and 90% respectively.

A striking observation of our study was high percentage of Mantoux positivity and X-Ray positivity in

group A, suggesting that our clinical diagnosis of TBM was substantiated by these two tests, barring the CSF examination which prompted us to do the precipitation test in these cases to confirm the diagnosis of TBM.

Ophthalmological examination which was done in each and every case revealed the changes of papilloedema and primary optic atrophy in 16% and 8% of cases in group A, while it was seen in 6% and 8% cases in group B. None of the cases showed evidence of papillitis and surprisingly none of cases in pyogenic group showed the evidence of papillitis, papilloedema and primary optic atrophy. The incidence of these changes on fundus examination have been reported differently by various workers in this field.

Our findings of optic atrophy and papilloedema in the total TBM group as such viz. 9.3% and 8% respectively are more or less similar to that reported by Verma et al (1966) & Thapar et al (1968). However, these two workers have also reported papillitis in 12.3% and 25% cases respectively in their series. Mishra (1962) and Udani (1974) in their series however noted a higher percentage of primary optic atrophy viz. 21.66% and 14.2% than that reported in our series. Udani et al however have not commented on the findings of papilloedema except stating that papilloedema may be found in very late stages of disease. Barring Verma (1966) who reported choroid

tubercles in 1.5% cases, none of the workers including us, observed findings of choroid tubercles in their series.

A detailed physical, biochemical and cytological examination of CSF depicted in Table XIII reveals certain interesting aspects. In both groups of cases of tuberculous meningitis, CSF was found to be clear on physical examination in 96% and 100% cases. Turbidity was observed only in 4% cases in group A (TBM group) as against 44% in cases of pyogenic meningitis (group C). None of our cases in TBM group had any coagulum formation. Udani et al (1974) have shown clear to turbid appearance of CSF in cases of tuberculous meningitis. Upadhyaya et al (1984) and Gupta et al (1990) in later study, however, reported turbidity in 50% and 72% of cases in TBM. Since most of our cases in TBM group had total cellular content between 5 - 100 cells/c.mm, turbidity was not found to be a common feature in our series.

As already stated, group A consisted of 25 cases in which CSF findings were not consistant to the clinical diagnosis of TBM. Here it was observed, that many of the cases had either normal protein, or a very high protein content and sugar was found to be normal or markedly decreased. Similarly, these cases had a mixed cellular content and some even had polymorphonuclear leucocytosis in CSF, as against the typical findings of lymphocytosis

which is a common picture of CSF in cases of TBM. Most of the cases viz. 40% had protein content between 100-500 mg%, but a significant proportion of these cases viz. 24% and 20% had normal values (15-45 mg%) and very high protein content (7500 mg%). Similarly, 40% of group A cases had normal sugar values while 32% had sugar below 20 mg%, which is not a typical picture of CSF seen in cases of TBM. Another important finding in CSF which doubted the diagnosis of TBM, was the presence of both lymphocytes and polymorphs in a very high percentage viz. 64% in group A.

Upadhyaya et al (1984) who also did precipitation test for early diagnosis of tuberculous meningitis experienced diagnostic difficulty in 25% cases of TBM where cytological findings were not correlating to the biochemical finding and clinical diagnosis of TBM. However, they have not reported the different biochemical and cytological findings in detail in groupwise manner, hence comparison with our findings could not be done.

Gupta et al (1990) however like us, studied 50 cases in which the CSF findings were not consistant with clinical diagnosis of TBM. They reported normal protein like us, in 24% of cases, normal sugar in 10% and markedly decrease sugar level in 16% of cases, as against 40% and 32% as reported by us. They too, like us, reported mixed picture of lymphocytes and polymorphs in CSF in 56% of cases. Although 16% of our cases in group A showed only

polymorphonuclear leucocytosis, Gupta et al reported this finding only in 8% cases.

Group B, which comprised of 50 cases in our study, revealed more or less typical findings in CSF, consistent to the diagnosis of TBM. It was seen that 64% of cases had protein values between 100 - 500 mg%, 72% had sugar values between 20 - 45 mg%, 54% showed decreased chloride content and all the cases (100%) had only lymphocytosis in CSF. In this group of cases, as against group A, where 20% cases had protein more than 500 mg%, there was not even a single case having protein more than 500 mg%. Whereas 32% of cases in group A had sugar below 20 mg% in group B (typical TBM cases) only 12% cases had sugar values below 20 mg%.

Gupta et al (1990) however reported 96% of cases in group B to have protein more than 100 mg%. However, in group B, though we reported only 12% cases having sugar less than 20 mg%, Gupta et al (1990) observed 34% cases having sugar content below 20 mg%. Another difference between his work and that of ours was that, whereas 100% of the cases in our series had only lymphocytes, 60% cases reported by Gupta et al (1990) had only lymphocytes, 36% had combined polymorphs with lymphocytes and 4% had only polymorphonuclear Leucocytosis.

The CSF findings in group C (pyogenic group) were typical of that of pyogenic meningitis and detailed

findings in this group are depicted in Table XIII. Though 24% of our cases in group C had protein more than 500 mg% & 72% of cases had sugar values below 20 mg%, it is surprising, that Gupta et al (1990) did not find a single case in these two categories of biochemical values.

The primary aim of our study was to perform the precipitation test in the cases of tuberculous meningitis and to arrive at an early diagnosis specially in those cases of TBM whose CSF findings were not in favour of clinical diagnosis of TBM, as well as to ascertain its values in differentiating cases of pyogenic meningitis from cases of tuberculous meningitis.

An important significant finding observed by us was, that in group A where CSF findings were not consistent with clinical diagnosis of TBM, 24 out of 25 cases (96%) showed a positive precipitation test whereas only one case in this group had a negative reaction. Similarly we observed that in group B, where clinical diagnosis and CSF findings were in favour of TBM, 49 out of the 50 cases (98%) showed a positive precipitation test, whereas only one case had a negative reaction. The precipitation test was however found to be negative in all 25 cases of pyogenic meningitis in group C in which the sediment in the sulfosalicylic tube was the three times than the sediment observed in the tube containing mercuric chloride.

The significance of the precipitation test in the early diagnosis of TBM can very well be gauged by our observation, that the precipitation test was positive in 96% of the dubious cases of TBM, where the CSF picture were confusing and not correlating to the clinical diagnosis. This test therefore helped us not only in diagnosing the cases of TBM early, but gave a direction to us for prompt therapeutic intervention.

Upadhyaya et al (1984) performed this test in 60 cases of TBM of which 30 cases (25% of total 120 cases) were those where the cytological and biochemical findings were not correlating with the clinical diagnosis of TBM (group A) and 30 cases were those in which CSF findings were in correlation of the clinical diagnosis of TBM. Another 15 cases in which he performed this test were cases of pyogenic meningitis. They also observed a positive precipitation test in 86.5% of group A cases, which however was slightly less than the positive reaction observed by us. Similarly in group B he found the test to be positive in 93.5% of cases, as against 98% observed in our study. Although the precipitation test was found to be negative in 100% of cases of pyogenic meningitis in our study, Upadhyaya et al (1984) found a negative test in 86.5% of cases in group C.

Gupta et al (1990) were the only other workers to have performed precipitation test in 125 cases of

meningitis. They observed that of the 50 cases which comprised their group A, 46 cases (92%) showed a positive precipitation test, whereas 8% had negative precipitation test and hence remained undiagnosed by this test. However, in group B which also comprised of 50 cases, they reported 96% positivity with this test and only 4% showed a negative response. Out of all the 25 cases in group C in their study, Gupta et al reported this test to be negative in 96% cases, whereas only 1 case in this group had a positive response.

In nutshell, on comparison of the results of precipitation test observed by us and that reported by Upadhyaya et al (1984) and Gupta et al (1990), it is amply clear, that the precipitation test is a quite sensitive, reliable, easy to perform, and less time consuming not only for the early diagnosis of cases of TBM but also to diagnose those cases of TBM where the CSF findings are dubious and confusing.

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SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

The present study was conducted in the Department of Paediatrics, M.L.B. Medical College, Jhansi, over a period of one year from March 1991 to February 1992.

The study was primarily aimed to evaluate the role of precipitation test in the early diagnosis of TBM, in differentiating cases of pyogenic meningitis and other forms of meningitis from the TBM group and more importantly to assess the significance of precipitation test in the diagnosis of those cases of TBM where the CSF findings were not consonant to the clinical diagnosis of TBM. Study was also aimed to find the incidence of TBM, mode of onset, various clinical features and to carry a detailed neurological examination in each and every case. Accordingly with these objectives in view, our case material was selected and broadly divided into three groups.

A total of 100 cases of meningitis were examined in the present study and were categorised into three groups.

Group A : This group comprised of 25 cases where the CSF findings were not correlating to clinical diagnosis of TBM.

Group B : This group comprised of 50 cases where the CSF findings were correlating to clinical diagnosis of TBM. This group acted as positive control.

Group C : This group comprised of 25 cases. Here the CSF findings and clinical diagnosis were in favour of pyogenic meningitis and other types of meningitis except TBM. This group acted as negative control.

Following is a brief summary of our observations.

I. Incidence :

The incidence of TBM, of the total paediatric admissions was observed to be 1.7%, which in turn reflects the incidence of Neuro-tuberculosis in Bundelkhand region.

II. Age and Sex Incidence :

It was observed that the highest incidence of TBM in both group A & B was in the age group 1-3 yrs, viz. 52% & 38% respectively. A significant finding was that 24% cases of TBM in both groups presented below 1 yr of age and the incidence decreased with increasing age of the patient. On the contrary, in pyogenic meningitis the highest incidence was observed between 7-12 yrs of age.

Regarding sex, our observations revealed that in all the groups male predominated and the incidence was found to be much higher than females.

III. Mode of onset :

TBM is a disease which has variable mode of onset and this has been highlighted in our study. It was seen that most of the patients in TBM group had either subacute or chronic mode of onset. In group A, 52% cases had chronic mode of onset, 44% had subacute onset, whereas only 4% cases presented atypically where the mode of onset was acute. Similarly in group B, it was observed that the mode of onset was subacute and chronic in 54% and 40% cases respectively, whereas 6% cases in this group presented atypically as acute cases. On the other hand, in pyogenic group maximum number of patients had acute (64%) onset and only 36% had subacute mode of onset.

IV. Clinical Features :

Regarding clinical features, it was seen that fever, convulsions, unconsciousness and vomiting were commonest clinical features in decreasing incidence in our study.

We observed that fever was present in 100% cases in all the three groups, while vomiting was present in 64% cases of TBM group and 80% in pyogenic group.

Unconsciousness was present in 80% cases of the TBM group and 76% of cases in pyogenic group, convulsions were noticed in 88% of cases in each group A and C, while in group B it was present in 94% of cases. Headache was noticed in children above the age of 3 yrs and was more common (36%) in pyogenic group than that observed in TBM group (30%).

V. Past history and History of Contact :

Relevant past history was recorded in all the cases with special emphasis to elicit the history of contact, history of measles and history of whooping cough.

It was seen that 52% patients in group A had a obvious history of contact, while it was present only in 30% of cases in group B. Similarly, past history of measles was elicited in 28% of cases in group A and 14% in group B. Only 2% cases in group B had a prior history of whooping cough.

VI. Association of Malnutrition in study groups :

It was also our endeavour to assess the degree of malnutrition in our study according to the classification of Indian Academy of Paediatrics (1972).

We observed that all the cases in TBM group had varying degree of malnutrition, while in pyogenic group 5 cases had normal nutrition. Since most of the cases in

group A and B (TBM group) had subacute and chronic mode of onset and had been ill for many weeks, it was seen that 52% and 54% cases respectively belonged to Grade II and 24% belonged to grade III.

A significant finding observed was, that none of the cases in pyogenic group had grade IV malnutrition. It was however present in 8% and 12% cases in group A and B.

VII. Important Clinical Findings in Study groups :

Majority of cases in TBM group (81%) had mild degree of anaemia, while it was present only in 40% cases in pyogenic group. Similarly, lymphadenopathy was found to be two times more common in TBM group (37%) than pyogenic group (16%), while hepatomegaly and spleenomegaly were present in 38.6% and 13% in TBM group and 32% and 8% in pyogenic group.

Further we observed that signs of meningeal irritation were present in greater number of cases of pyogenic meningitis (96%), as against (74%) seen in TBM group.

A detailed cranial nerve examination was performed in all the cases. Our observations revealed that cranial nerve involvement was seen in 24% cases in TBM group, while it was present only in 8% in pyogenic group. It was seen that commonest cranial nerve involvement was

VIIth nerve, followed by VIth and IIIrd nerve in TBM group. Motor deficit (predominantly hemiplegia) was found in 24% of cases in TBM group, as against 4% cases in pyogenic group.

It was seen that 38.6% cases in TBM group had grade III coma followed by grade II coma in 29.3%, grade I coma in 9.3% of cases and grade IV coma in only 2.6%, while in pyogenic group most of the cases, 48% were admitted in grade II coma followed by 16% and 12% in grade I and III coma respectively.

VIII. Investigations :

(1) Haematological : In our study we found that mean total leucocyte count in the pyogenic group was higher and statistically significant (p value < 0.05) than the values observed in both groups of TBM. Further, it was seen that there was lymphocytosis in TBM group and polymorphonuclear leucocytosis in pyogenic group, and values were found to be statistically significant (p value < 0.001).

Regarding mean haemoglobin values it was observed that cases of pyogenic meningitis (group C) had higher mean values, than both group A and B and values were found to be significant (p value < 0.001). However, no statistically significant difference was seen in mean haemoglobin values between group A and B (p value > 0.05).

The mean ESR on the other hand was highest in group B though no statistical difference was seen in mean ESR values between group A and B ($p_{AB} > 0.05$). However in group C, ESR was found to be much lower than TBM groups, values being statistically significant ($p_{AC} < 0.05$, $p_{BC} < 0.01$).

(2) Mantoux Test and X-Ray Chest :

The overall Mantoux positivity in cases of TBM, (both group A and B) was 34%, though it was slightly higher in group A (40%) than in group B (32%).

X-Ray findings consistant to the diagnosis of primary tuberculosis was observed in 60% cases in TBM group, of which 76% cases were positive in group A and 52% cases were positive in group B.

(3) Ophthalmological Examination :

Ophthalmological examination was done in each and every case to observe the findings of papillitis, papilloedema and primary optic atrophy. It was seen that in group A, 8% cases had optic atrophy, while 16% had papilloedema. Similarly, primary optic atrophy and papilloedema were observed in 8% and 6% cases in group B respectively and none of the case in group A and B had papillitis. Cases of pyogenic meningitis in contrast revealed no abnormality.

(4) CSF Examination :

A detailed physical, biochemical and cytological examination of CSF was done in each and every group of cases. On CSF examination we observed that CSF was clear in 96% and 100% of cases in group A and B respectively. Turbidity was observed only in 4% cases in group A (TBM group) as against 44% in cases of pyogenic meningitis (group C).

Most of the cases in group A viz., 40% had protein content between 100-500 mg%, but a significant proportion of these cases viz., 24% had normal values (15-45 mg%) whereas 20% cases had a very high protein content (7500 mg%). Similarly, 40% of group A cases had normal sugar values, while 32% had sugar below 20 mg%. In 64% of cases we found presence of both lymphocytes and polymorphs in group A, while 16% had polymorphonuclear leucocytosis and only 20% of these cases had a usual picture of lymphocytes.

Group B cases, revealed more or less typical findings in CSF consistent to the diagnosis of TBM. 64% of these cases had protein content of 100-500 mg%, 34% of cases had levels ranging between 45-100, whereas in this group we had only 1 case (2%) which showed normal protein content (15-45%). In this group 36 out of the 50 cases had decreased sugar level, ranging from 20-45 mg%, while 12% of cases had extremely low levels viz., 20 mg%. However, 16% of cases had normal CSF sugar level.

All the cases (100%) in this group had only lymphocytes in the CSF.

The CSF findings in group C (pyogenic group) were typical of that of pyogenic meningitis.

(5) Precipitation Test :

The primary aim of our study was to perform the precipitation test in the cases of tuberculous meningitis and to arrive at an early diagnosis specially in those cases of TBM whose CSF findings were not in favour of clinical diagnosis of TBM, as well as to ascertain its values in differentiating cases of pyogenic meningitis from cases of tuberculous meningitis.

An important significant finding observed by us was that in group A, where CSF findings were not consistent with clinical diagnosis of TBM, 24 out of 25 cases (96%) showed a positive precipitation test. Similarly in group B where clinical diagnosis and CSF findings were in favour of TBM, 49 out of 50 cases (98%) showed a positive precipitation test, whereas only one case had a negative reaction. The precipitation test was however found to be negative in all 25 cases of pyogenic meningitis in group C.

The significance of the precipitation test is the early diagnosis of TBM can very well be gauged by our observation that it was positive in 96% of the

dubious cases of TBM where CSF picture was not correlating to the clinical diagnosis of TBM.

In nutshell, we concluded that the precipitation test is quite simple, reliable, sensitive, easy to perform, less time consuming for the early detection of tuberculous meningitis, as well as to differentiate the cases of pyogenic meningitis from that of tuberculous meningitis.

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A P P E N D I X

APPENDIX

Working Proforma

Department of Paediatrics,
M.L.B. Medical College & Hospital, Jhansi (U.P.)

Topic : PRECIPITATION TEST : ITS EVALUATION FOR EARLY DIAGNOSIS OF TUBERCULOUS MENINGITIS.

Guide : Dr. R.S. Sethi, M.D., D.C.H., Assistant Professor in Paediatrics,

Investigator : Dr. P.K. Bansal.

Case No. :

Dated :

MRD No. :

Ward/Bed No. :

Details of Patients :

Name :

Age/Sex :

Address :

Date of admission :

Date of discharge :

Chief complaints :

a) Fever : Duration :
Severity : Mild/high
Type : Continuous/intermittent/remittent.
Association :

b) Cough : Duration
With or without expectoration
Amount of sputum
Mucoid/Purulent/Mucopurulent
Hemoptysis

c) Loss of weight :
- Duration
- Amount

d) Failure to thrive : Yes / No Duration :

e) Appetite : Lost / Retained Duration :

f) Alternate constipation & Diarrhoea :

g) Swelling over neck : Yes / No

- Duration :
- Discharge :
- Pain :
- Association :

h) Ear discharge or any other Pyaemic focus : Present/Absent

i) Headache : Yes / No

j) Vomiting : Yes / No

k) Convulsions :

- Duration :
- Type :
- Associated factor :

l) Consciousness : Impaired / Intact

Other complaints :

History of past illness :

a) History of measles/ exanthematous fever/ pertussis/tuberculosis :

b) History of malnutrition :

c) Ch. Diarrhoea :

Family History :

- Tuberculosis :
- Any other illness :

Geniological History :

Dietary History :	Average intake at present	Expected for this age
- Calories :		
- Protein :		

Immunization History :

- B.C.G.
- D.P.T.
- Polio
- Measles

History of socio-economic status :

General Examination :

- G.C. :
- Pulse :
- Resp. Rate :
- B.P. :
- Temperature :
- Hydration :
- Icterus :
- Pallor / Anaemia :
- Oedema :
- Clubbing :
- Cyanosis :
- J.V.P. :
- Lymphadenopathy :
- Posture/attitude :
- Decubitus :
- Any other :
  - Hair :
  - Fontanelle :
  - Eyes :
  - Oral cavity :
  - Buccal Mucosa :
  - Teeth :
  - Skin :
  - Subcutaneous Fat :
  - Muscle mass :

Anthropometric Examination :

- Height :
- Weight :
- Head circumference :
- Mid arm circumference:

Grade of Malnutrition according to IAP classification

Systemic Examination :

a) C.N.S.

i) Higher centres

- Consciousness

Grade I
II
III
IV

ii) Cranial Nerve Examination

iii) Signs of Meningeal Irritation

iv) Speech Gair

v) Motor system :

- Bulk
- Tone
- Power
- Co-ordination
- Abnormal movements

vi) Sensory system

	Lt.	Rt.

vii) Reflexes

- Superficial
- Deep

INVESTIGATIONS :

Haematological : TLC DLC

ESR Hb

Radiological :

i) X-Ray chest/skull

ii) Mantoux Test

iii) Fundus Examination

iv) CSF . Cytobiochemical

v) Culture

vi) Precipitation Test

SUMMARY :

COMMENTS

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